## Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 39-46 and 49-51 were pending in this application and were rejected on various grounds. The rejections to the presently pending claims are respectfully traversed.

## Note of Change of Address

A revocation of power of attorney and change of address was filed on February 20, 2003 and received by the Patent Office in this case. Once again, the Examiner is respectfully requested to address all correspondence in this case to:

**Ginger Dreger, Heller Ehrman White & McAuliffe LLP,**
**275, Middlefield Road,**
**Menlo Park, CA 94025.**

## Claim Objections

6. Claims 39-44 are objected to because : claims 39-44 contain recitation of an "or" in section (c), which cannot be construed as a reference to an isolated polypeptide within the claimed group.

7. Claims 39-43 are objected for reciting "wherein, the nucleic acid" which appears to have a misplaced coma.

Applicants have amended these recitations appropriately and hence, this rejection should be withdrawn.

## Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 39-46 and 49-51 were rejected under 35 U.S.C. §101 allegedly "because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility."

Claims 39-46 and 49-51 are further rejected under 35 U.S.C. §112, first paragraph, allegedly since one skilled in the art would not know how to make and use the claimed invention.

The Examiner acknowledges the Applicants summary of the "Utility Guidelines and case law" but disagrees with the "interpretation of what constitutes a specific, substantial and credible utility." The Examiner asserts that "the increased copy of DNA does not provide a readily apparent use for the polypeptide PRO187 itself, for which no information regarding critical level of expression symptomatic of cancer, specific biological activity or role in cancer is disclosed". For the reasons discussed below, Applicants respectfully traverse.

*Utility – Legal Standard*

In interpreting the utility requirement, in *Brenner v. Manson* [1] the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form." [2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy." [3]

Later, in *Nelson v. Bowler* [4] the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility." [5]

In *Cross v. Iizuka* [6] the CAFC reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less

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[1] *Brenner v. Manson* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F. 2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between." [7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility." [8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face. [9] The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." [11], [12]

Compliance with 35 U.S.C. §101 is a question of fact. [13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. [14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely

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[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid*

[11] *In re* Langer, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (CCPA 1974).

[12] See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re* Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines") [15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "'substantial'" utility."' [16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, [17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

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[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01

[17] M.P.E.P. §2107 II (B) (1)

*Proper Application of the Legal Standard*

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the native sequence PRO187 polypeptide of SEQ ID NO:23.

In particular, the gene amplification assay discloses that the nucleic acid encoding PRO187 is significantly overexpressed in various human tumor tissues as compared to a non-cancerous human tissue control. Table 8 explicitly states that PRO187 is significantly overexpressed in lung and colon tumors as compared to the normal control. The specification further teaches that these data demonstrate that the PRO187 polypeptide of the present invention is also useful as a diagnostic marker for the presence of one or more cancerous tumors in which it is significantly overexpressed. The above disclosure is sufficient to establish a specific, substantial and credible utility for the PRO187 polypeptide.

The Examiner contends that "Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and olypeptide levels from the chromosomal region. Their approach to investigation gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time...The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region, which is highly amplified". The Examiner further alleges, "Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract)...." The Examiner also alleges that "Pollack *et al.* also used CGH technology concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack *et al.* also do not support the asserted utility of the claimed invention."

Applicants submit that, in Orntoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Orntoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Orntoft *et al* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a

cluster of genes having increased mRNA expression (see page 40). Orntoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Orntoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Orntoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Orntoft *et al.* clearly support Applicants position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

The Examiner indicates that Applicants have not indicated whether PRO187 is in a gene cluster region of a chromosome. But Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters and further, as discussed below, Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

The Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs were hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines were hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is

more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

The Examiner also alleges that the papers by Orntoft *et al.*, Hyman *et al.* and Pollack *et al.* "state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertion that the claimed PRO187 proteins have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial."

Applicants respectfully disagree.

As stated above, in explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions that **Office personnel must be careful not to interpret the phrase "immediate benefit to the public"** or similar formulations used in certain court decisions **to mean that products or services based on the claimed invention must be "currently available" to the public** in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a '"substantial" utility'"[18] (emphasis added). Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement states, "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of

ordinary skill in the art, do not impose a rejection based on lack of utility." Accordingly, Applicants respectfully submit that Applicants' assertion that the claimed PRO187 proteins have utility in the field of cancer diagnostics is substantial.

In support of utility, Applicants previously submitted a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, which discusses the correlation between mRNA expression and protein levels, and shows that mRNA expression correlates well with protein levels, in general, based on Dr. Polakis' vast experience of more than 20 years and based on the microarray analysis results of approximately 200 gene transcripts (mRNAs). Applicants maintain that the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard, the proper legal standard being only that the showing of correlation between mRNA and polypeptide levels be "more likely than not."

The Office Action states that the Dr. Polakis Declaration is insufficient to overcome the rejection "since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels and not gene amplification levels and protein levels". Applicants agree but indeed, if the Polakis Declaration were not relevant, then neither should the Hu *et al.* reference cited by the Examiner, since Hu also concerns the correlation between mRNA and protein levels (see discussions below).

Further, the Office action alleges that only Dr. Polakis' conclusions are provided in the Declaration. There was allegedly no evidentiary support to Dr. Polakis' statement that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide".

Applicants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human

tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew. [18] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument" [19] Furthermore, the Federal Court of Appeals held in *In re Alton*, "[w]e are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner" [20]. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines [21] which states that, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered". The statement in question from an expert in the field (the Polakis declaration) states: "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis declaration, this rejection is improper under both the case law and the Utility guidelines.

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[18] *In re Rinehart 531* F.2d 1084, 189 USPQ 143 (CCPA 1976) and *In re Piasecki* 745 F 2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

[19] *In re Alton* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker* 977 F 2d at 1445, u2 USPQ2d at 1444.

[20] *In re Alton*, supra.

[21] Part IIB, 66 Fed. Reg. 1098 (2001).

The Examiner cites Hu et al. for support that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease.

As a preliminary matter, it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants respectfully maintain that for the reasons previously set forth in the Applicants' response that Pennica *et al.* and Konopka do not show a lack of correlation between gene (DNA) amplification and elevated mRNA levels since they discuss WISP genes (Pennica) and the abl gene (Konopka) and do not discuss genes, in general.

Applicants further respectfully submit that the Hu et al. reference does not show a lack of correlation between gene amplification data and the biological significance of cancer genes.

First, the analysis by Hu et al. has certain statistical flaws. According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right

column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Secondly, Applicants submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules are overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusions based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al* admit that ., "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "[t]his may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added).

The Office Action also says that the Ashkenazi declaration is insufficient to overcome the instant rejection because "the Declaration provides only Dr. Ashkenazi's won conclusions and no references to scientific reasoning or any evidentiary clinical support...Argument o counsel cannot take the place of evidence lacking in the record".

Again, as discussed above in the Utility guidelines "it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." In Dr. Ashkenazi's opinion, even if the protein were no over-expressed, the simultaneous testing of gene amplification and gene product over-expression would enable more accurate tumor classification. To support this reasoning of Dr. Ashkenazi, Applicants had submitted the article by Hanna and Mornin, to demonstrate that, as in the example of the HER-2 gene, testing both gene and gene product (protein) lead to a more accurate classification of the cancer and more effective tumor treatment.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO187 polypeptide, for example, in detecting over-expression or absence of expression of PRO187. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Based on these discussions, one skilled in the art, would know how to use the claimed polypeptides as a lung or colon tumor marker, at the time the application was filed.

Thus, Applicants have demonstrated utility for the PRO187 polypeptide. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

## 35 USC § 112, First Paragraph/Written Description

Claims 39-43 have been rejected for alleged lack of sufficient written description.

*The Legal Test for Written Description*

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[22, 23] The adequacy of written description support is a

[22] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[23] *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

factual issue and is to be determined on a case-by-case basis.[24] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.[25,26]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[27] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field."[28] Further, the hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity, have the capability of understanding the scientific and engineering principles applicable to the pertinent art" (Emphasis added).[29, 30]

*The Disclosure Provides Sufficient Written Description for the Claimed Invention*

Applicants submit that the instant specification evidences the actual reduction to practice of a full-length PRO187 polypeptide of SEQ ID NO: 23, with or without its signal sequence. Thus, the genus of **native polypeptide sequences** with at least 80% sequence identity to SEQ ID NO: 23, and which possess the functional property "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors" would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

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24 *See, e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

25 *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

26 *See also* MPEP §2163 II(A).

27 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

28 *See also* MPEP §2141.03.

29 *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988).

30 *See also* MPEP §2141.03.

Applicants point out that the Specification describes methods for the determination of percent identity between two amino acid sequence. The Specification further describes methods for one of ordinary skill in the art to *identify* peptide sequences having at least 80% identity to SEQ ID NO: 23 'wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors' by testing the nucleic acids encoding these variants in the gene amplification assay which is well-described in Example 90 of the instant specification.

Applicants claim those **native peptide sequences** with 80-99% homology to SEQ ID NO: 23 and wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors. One of skill in the art could readily test these variant native polypeptide sequences to determine whether its encoding nucleic acid is amplified in lung or colon tumors based on the step-by-step methods set forth throughout the specification and in Example 90. There is no need to provide a description of the conserved regions of the polypeptide. Neither is there a need to correlate structure- to- function for the instantly claimed peptides or to identify specific sites at which variability is tolerated. The rejection based on difficulty in structure-function prediction in the art is irrelevant here, since Applicants are not predicting function of the variant native polypeptide sequences of SEQ ID NO: 23. Instead, Applicants claim those peptides with these prerequisites: 1) 80-99% homology to SEQ ID NO: 23 and 2) which demonstrate a well-defined function, namely, whose encoding nucleic acids are amplified in the gene amplification assay.

Accordingly, the specification provides adequate written description for native polypeptide sequences having at least 80% identity to SEQ ID NO: 23 wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors. For the above reasons, Applicants respectfully request that the rejection be withdrawn and the claims be allowed.

The Examiner is therefore respectfully requested to reconsider and withdraw the present rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: May 6, 2005

Daphne Reddy

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